

Dean L. Engelhardt, et al.
Serial No.: 08/486,069

Filed: June 7, 1995

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(37 CFR 1.121) For Entry of Applicants' March 9, 2001 Amendment Under
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Clean Version of Replacement Claims

1 569. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;
subjecting said detectable non-radioactively labeled fragments to a sequencing gel to separate or resolve said fragments; and
detecting non-radioactively the presence of each of said separated or resolved fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

2 586. (Twice Amended) The process according to claim 569, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

3 587. (Amended) The process according to claim 569, wherein said providing or generating step, the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

588. (Amended) The process according to claim 587, wherein at least one of said non-radioactively modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

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X4
600. (Amended) The process according to claim 569, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

Enz-5(D8)(C2)

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(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein Sig is covalently attached to PM directly or through a linkage group.

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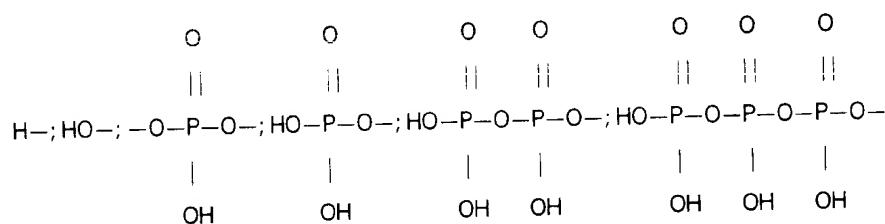
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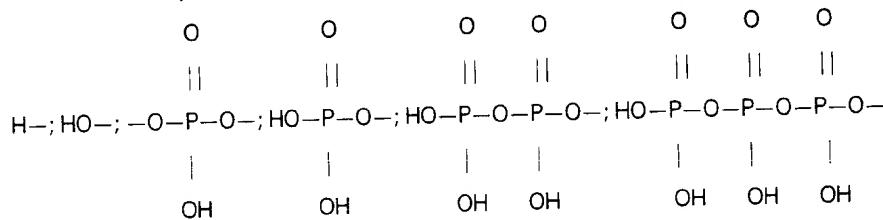
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wherein B and A are covalently attached directly or through a linkage group,
wherein if B is a purine or a purine analog, A is attached to the 8-position of the
purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is
attached to the 7-position of the deazapurine or deazapurine analog, and if B is a
pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine
or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and
HO- .

602. (Amended) The process according to claim 601, wherein y and z
are H- .

624. (Amended) The process according to claim 621, wherein said linkage group
does not substantially interfere with formation of the signaling moiety or detection
of the detectable non-radioactive signal.

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X6
713. (Amended) The process according to claim 709, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

714. (Amended) The process according to claim 713, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

X7
716. (Twice Amended) The process according to claims 569, 600 or 601, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

X8
719. (Twice Amended) The process according to claim 569, wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs are capable of being detected non-radioactively by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X9
720. (Amended) The process according to claim 569, wherein said detecting step comprises localizing said non-radioactively labeled nucleic acid fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs.

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721. (Twice Amended) A process for determining the sequence of a nucleic acid
of interest, comprising the steps of:

X¹⁰ providing or generating detectable non-radioactively labeled nucleic acid
fragments, each fragment comprising a sequence complementary to said nucleic
acid of interest or to a portion thereof, wherein each of said fragments comprises
one or more detectable non-radioactively modified or labeled nucleotides or
nucleotide analogs, which nucleotide analogs can be attached to or coupled to or
incorporated into DNA or RNA, and wherein said one or more detectable non-
radioactively modified or labeled nucleotides or nucleotide analogs have been
modified or labeled on at least one of the sugar moiety, the sugar analog, the
phosphate moiety, the phosphate analog, the base moiety, or the base analog
thereof;

introducing or subjecting said detectable non-radioactively labeled fragments
to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and
detecting non-radioactively each of the separated or resolved fragments; and
determining the sequence of said nucleic acid of interest.

X¹¹ 738. (Twice Amended) The process according to claim 721, wherein the
detectable non-radioactively labeled complementary nucleic acid is fragmented prior
to separation in said sequencing gel.

X¹² 739. (Amended) The process according to claim 721, wherein said providing or
generating step, the one or more non-radioactively modified or labeled nucleotides
or nucleotide analogs have been incorporated into said nucleic acid fragment or
fragments.

740. (Amended) The process according to claim 739, wherein at least one of said
non-radioactively modified or labeled nucleotides or nucleotide analogs is at a
terminus of said fragment or fragments.

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X13
752. (Amended) The process according to claim 721, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety

or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to BASE directly or through a linkage group at a position
other than the C5 position when BASE is a pyrimidine moiety or an analog thereof,
at a position other than the C8 position when BASE is a purine moiety or an analog
thereof and at a position other than the C7 position when BASE is a 7-deazapurine
moiety or an analog thereof;

- (ii) a nucleotide or nucleotide analog having the formula

Sig

|

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to SM directly or through a linkage group; and

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(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

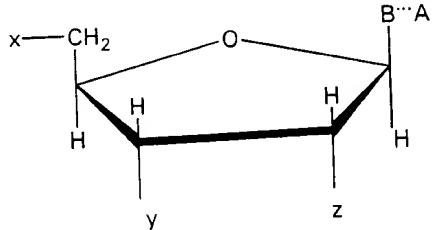
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to PM directly or through a linkage group.

753. (Amended) The process according to claim 721, wherein in said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the moiety, or an analog of any of the foregoing, provided that whenever B is a C1'-position of the sugar moiety or sugar analog, the purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

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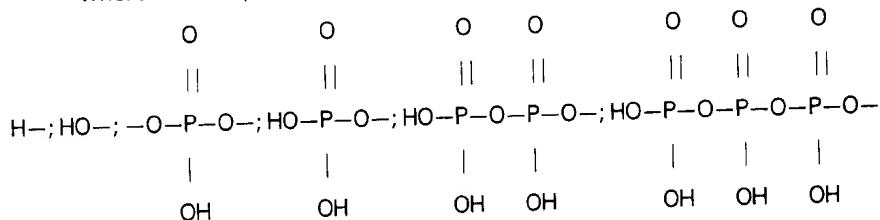
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wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

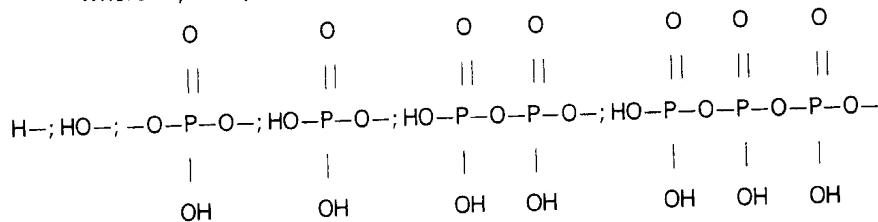
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO- .

3

754. (Amended) The process according to claim 753, wherein y and z are H- .

4

776. (Amended) The process according to claim 773, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

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X15
859. (Twice Amended) The process according to claim 721, wherein said
detectable non-radioactively labeled nucleic acid fragments are detectable by a non-
radioactive means selected from the group consisting of a fluorescent
measurement, a chemiluminescent measurement, and a combination thereof.

X16
866. (Amended) The process according to claim 865, wherein in said detecting
step the directly detectable signal comprises a member selected from the group
consisting of a chelating compound, a fluorogenic compound, a chromogenic
compound, a chemiluminescent compound and an electron dense compound.

X17
868. (Amended) The process according to claims 721, 752 or 753, wherein said
detecting step is carried out by means of an indirectly detectable signal provided by
said one or more non-radioactively modified or labeled nucleotides or nucleotide
analog, said A or said Sig detectable non-radioactive moiety.

X18
871. (Twice Amended) The process according to claim 721, wherein said one or
more modified or labeled nucleotides or nucleotide analogs are capable of being
detected by a member selected from the group consisting of an enzymatic
measurement, a fluorescent measurement, a chemiluminescent measurement, a
microscopic measurement and an electron density measurement.

X19
872. (Twice Amended) The process according to claim 721, wherein said
detecting step comprises localizing said detectable non-radioactive labeled nucleic
acid fragments by means of said one or more non-radioactive modified or labeled
nucleotides or nucleotide analogs.

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873. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

detecting non-radioactively the detectable non-radioactive labeled nucleic acid fragments with a sequencing gel; and
determining the sequence of said nucleic acid of interest.

X 19

X 20

890. (Twice Amended) The process according to claim 873, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented and separated prior to detecting in said sequencing gel.

X 21

891. (Amended) The process according to claim 873, wherein in said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

892. (Amended) The process according to claim 891, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

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X22
904. (Amended) The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety

or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

- (ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

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(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

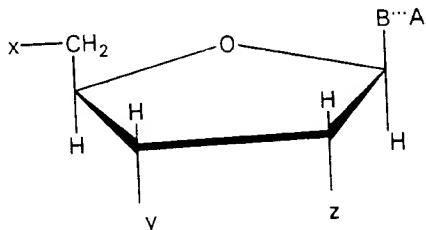
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM directly or through a linkage group.
Sig is covalently attached to PM directly or through a linkage group.

905. (Amended) The process according to claim 873, wherein in said providing or
generating step, the non-radioactive modified or labeled nucleotides or nucleotide
analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine
moiety or an analog of any of the foregoing, and B is covalently bonded to the C1'
position of the sugar moiety or sugar analog, provided that whenever B is a purine,
a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar
moiety or sugar analog is attached at the N9 position of the purine moiety, the
purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and
whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or
the sugar analog is attached at the N1 position of the pyrimidine moiety or the
pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one
component of a signalling moiety capable of producing directly or indirectly a
detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group.

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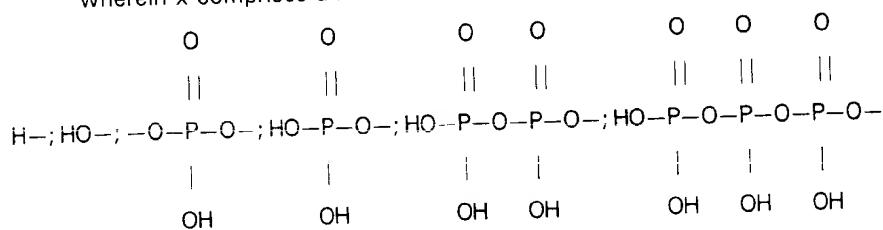
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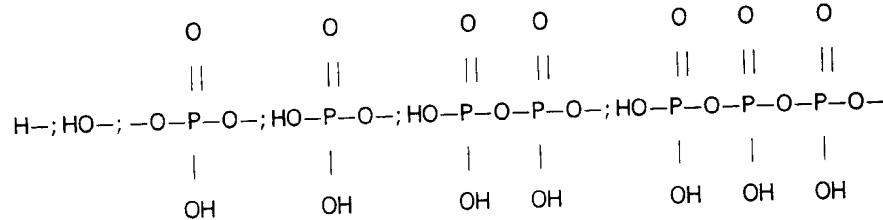
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wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO-.

f2
906. (Amended) The process according to claim 905, wherein y and z are H- .

f2
928. (Amended) The process according to claim 925, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

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X24
1011. (Twice Amended) The process according to claim 873, wherein said
detectable non-radioactive labeled nucleic acid fragments are detectable by a non-
radioactive means selected from the group consisting of a fluorescent
measurement, a chemiluminescent measurement, and a combination thereof.

1012. (Twice Amended) The process according to claim 873, wherein said
detecting step, the detectable non-radioactive labeled nucleic acid fragments are
separated or resolved electrophoretically.

X25
1017. (Amended) The process according to claim 1016, wherein said detecting
step is carried out by means of a directly detectable signal provided by said one or
more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A
or said Sig detectable non-radioactive moiety.

1018. (Amended) The process according to claim 1013, wherein said detecting
step the directly detectable signal comprises a member selected from the group
consisting of a chelating compound, a fluorogenic compound, a chromogenic
compound, a chemiluminescent compound and an electron dense compound.

X26
1020. (Amended) The process according to claims 873, 904 or 905, wherein said
detecting step is carried out by means of an indirectly detectable signal provided by
said one or more non-radioactive modified or labeled nucleotides or nucleotide
analog, said A or said Sig detectable non-radioactive moiety.

X27
1023. (Twice Amended) The process according to claim 873, wherein said one or
more non-radioactive modified or labeled nucleotides or nucleotide analogs are
capable of being detected by a member selected from the group consisting of an
enzymatic measurement, a fluorescent measurement, a chemiluminescent
measurement, a microscopic measurement and an electron density measurement.

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X²⁸
1024. (Twice Amended) The process according to claim 873, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

1025. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting non-radioactively with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.
SUB (II)

X²⁹
1042. (Twice Amended) The process according to claim 1025, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

X³⁰ SUB (C)
1043. (Amended) The process according to claim 1025, wherein said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

1044. (Amended) The process according to claim 1043, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

X 31
~~1056. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:~~

- ~~(i) a nucleotide or nucleotide analog having the formula~~

~~PM—SM—BASE—Sig~~

~~wherein~~

~~PM is a phosphate moiety or phosphate analog,~~

~~SM is a sugar moiety or sugar analog,~~

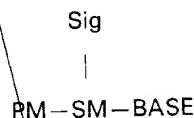
~~BASE is a pyrimidine, a purine or a 7-deazapurine base moiety~~

~~or a base analog of any of the foregoing; and~~

~~Sig is a detectable non-radioactive moiety,~~

~~wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;~~

- ~~(ii) a nucleotide or nucleotide analog having the formula~~



~~wherein~~

~~PM is a phosphate moiety or phosphate analog,~~

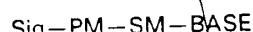
~~SM is a sugar moiety or sugar analog,~~

~~BASE is a base moiety or base analog, and~~

~~Sig is a detectable non-radioactive moiety,~~

~~wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and~~

- ~~(iii) a nucleotide or nucleotide analog, said nucleotide having the formula~~



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wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

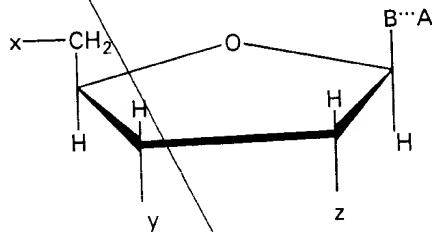
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to PM directly or through a linkage group.

1057. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group,

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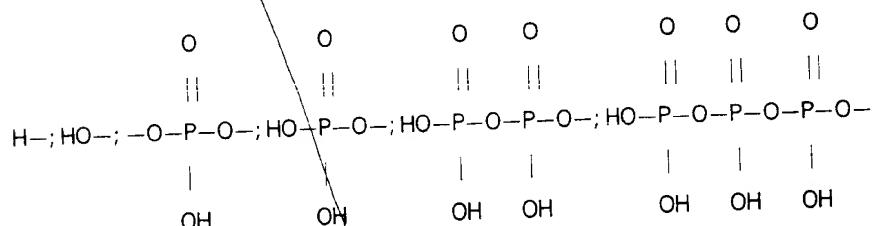
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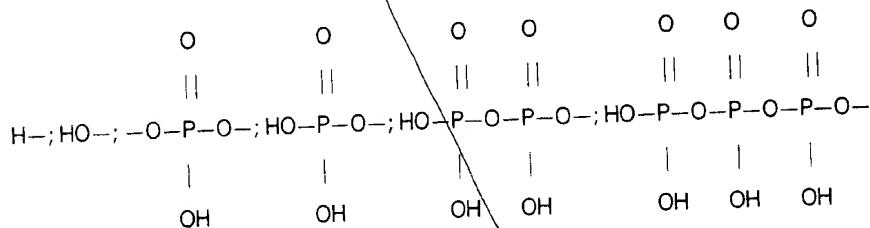
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wherein if B is a purine or a purine analog, A is attached to the 8-position of
the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is
attached to the 7-position of the deazapurine or deazapurine analog, and if B is a
pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine
or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and
HO-.

1058. (Amended) The process according to claim 1057, wherein y and z
are H- .

1164. (Twice Amended) The process according to claim 1025, wherein said
detecting step, the detectable non-radioactive labeled nucleic acid fragments are
separated or resolved electrophoretically.

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1169. (Amended) The process according to claim 1165, wherein said detecting
~~X 33~~ step is carried out by means of a directly detectable signal provided by said one or
more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A
or said Sig detectable non-radioactive moiety.

1170. (Amended) The process according to claim 1165, wherein said detecting
step the directly detectable signal comprises a member selected from the group
consisting of a chelating compound, a fluorogenic compound, a chromogenic
compound, a chemiluminescent compound and an electron dense compound.

~~X 34~~ 1172. (Amended) The process according to claims 1025, 1056 or 1057, wherein
said detecting step is carried out by means of an indirectly detectable signal
provided by said one or more non-radioactive modified or labeled nucleotides or
nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

~~X 35~~ 1175. (Twice Amended) The process according to claim 1025, wherein said one
or more modified or labeled nucleotides or nucleotide analogs are capable of being
detected by a member selected from the group consisting of an enzymatic
measurement, a fluorescent measurement, a chemiluminescent measurement, a
microscopic measurement and an electron density measurement.

~~X 36~~ 1176. (Twice Amended) The process according to claim 1025, wherein said
detecting step comprises localizing said detectable non-radioactive labeled nucleic
acid fragments by means of said one or more modified or labeled nucleotides or
nucleotide analogs.

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1177. (Twice Amended) A process for determining with a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid of interest or a portion thereof, said process comprising the steps of:

(A) providing

- (i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid; or
- (ii) one or more oligonucleotides or polynucleotides comprising at least one said detectable non-radioactive chemically modified or labeled nucleotide or nucleotide analog; or
- (iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one chemically modified or labeled nucleotide or nucleotide analogs (ii), or both (i) and (ii), into one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof and said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

X36

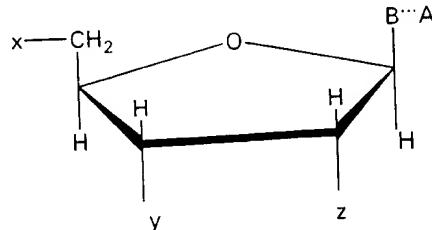
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(i)

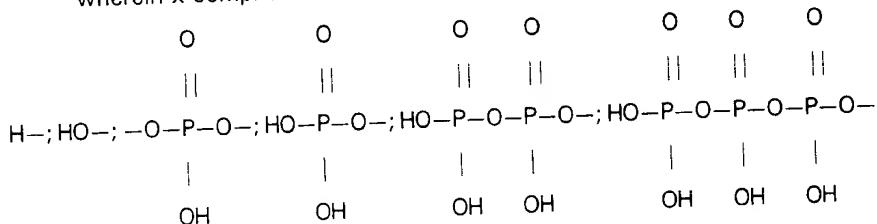


wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

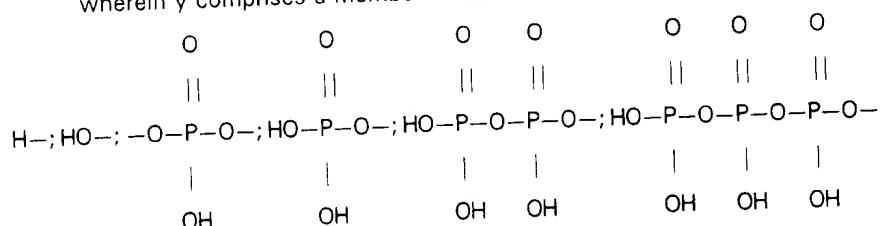
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



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wherein z comprises a member selected from the group consisting of H- and
HO-;

(ii)

Sig

|

PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to
wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and
SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said detectable non-radioactive labeled
fragments to a sequencing gel;

X 34
(D) separating or resolving said detectable non-radioactive labeled
fragments; and

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(E) non-radioactively detecting directly or indirectly the presence of said detectable non-radioactive labeled fragments to determine the sequence of said nucleic acid of interest.

37
1281. (Twice Amended) The process according to claim 1177, wherein said detectable non-radioactive labeled nucleic acid fragment or fragments are terminally ligated or attached to a polypeptide.

38
1291. (Amended) The process according to claim 1290, wherein said detecting step the directly detectable signal providing A or Sig detectable non-radioactive moiety comprises a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

39
1297. (Twice Amended) The process according to claim 1177, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

40
1298. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more detectable non-radioactive labeled oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

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- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base

analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to BASE directly or through a linkage group at a position
other than the C5 position when BASE is a pyrimidine moiety or an analog thereof,
at a position other than the C8 position when BASE is a purine moiety or an analog
thereof and at a position other than the C7 position when BASE is a 7-deazapurine
moiety or an analog thereof, and such covalent attachment does not substantially
interfere with double helix formation or nucleic acid hybridization;

- (ii) a nucleotide or nucleotide analog having the formula

Sig
|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached
to SM, and Sig is covalently attached to SM directly or through a linkage group and
such covalent attachment does not substantially interfere with double helix
formation or nucleic acid hybridization; and

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(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to PM directly or through a linkage group, and such
covalent attachment does not substantially interfere with double helix formation or
nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog (iii) is attached to an
oligonucleotide or a polyribonucleotide, and provided that when Sig is attached
through a chemical linkage to a terminal PM at the 3' position of a terminal
ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal
oxidation of a 3' terminal ribonucleotide previously attached to said
oligonucleotide or polyribonucleotide; and

X40
(b) detecting non-radioactively the presence of said Sig detectable non-
radioactive moieties in any of the detectable non-radioactive labeled oligo- or
polynucleotides which have hybridized to said nucleic acid of interest.

X41
1340. (Amended) The process according to claim 1298, wherein said covalent
attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with
the characteristic ability of Sig to form a detectable non-radioactive signal.

X42
1349. (Amended) The process according to claim 1345, wherein said linkage
group does not substantially interfere with formation of the signaling moiety or
detection of the detectable non-radioactive signal.

X43 1405. (Amended) The process according to claim 1403, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

X44 1409. (Twice Amended) The process according to claim 1298, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X45 1411. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

- (i) an oligo- or polynucleotide complementary to and capable of (1) specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein; and
- (ii) a non-radioactively detectable protein which is capable of binding to or complexing with said nucleic acid hybrid;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex; and

(C) detecting non-radioactively the presence of said non-radioactively detectable protein in said complex to detect said nucleic acid of interest.

X46 Sub (cc) 50 1430. (Amended) The process according to claim 1411, wherein said oligo- or polynucleotide (i) comprises at least one protein binding nucleic acid sequence selected from the group consisting of an antibody, a promoter, a repressor and an inducer.

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X47
1432. (Amended) The process according to claim 1430, wherein said at least one protein binding nucleic acid sequence is covalently attached to said oligo- or polynucleotide.

X48
1434. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to bind to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

1435. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to be detected non-radioactively when bound to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

X49
1448. (Amended) The process according to claim 1446, wherein said signaling component or indicator molecule comprises an aliphatic chemical moiety comprising at least four carbon atoms.

X50
1468. (Amended) The process according to claims 1467, wherein said direct detection step is carried out by a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound, an enzyme, a radioactive compound and an electron dense compound.

X51
1471. (Twice Amended) The process according to claim 1411, wherein said nonradioactively detectable protein is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

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1473. (Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

X52
contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

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(ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to
SM, and Sig is covalently attached to PM directly or through a linkage group,
SM, and Sig is covalently attached to PM directly or through a linkage group,

to permit specific hybridization of said clone or clones or DNA fragments or oligo-
or polynucleotides to the locus or loci of said particular chromosome;

X58
detecting non-radioactively any specifically hybridized clone or clones or DNA
fragments or oligo- or polynucleotides, and determining the number of copies of
said particular chromosome; and

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comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1474. (Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM-SM-BASE-Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

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(ii) a nucleotide or nucleotide analog having the formula

Sig

|

PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM directly or through a linkage group; and
Sig is covalently attached SM directly or through a linkage group;

(iii) a nucleotide or nucleotide analog having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM directly or through a linkage group;
Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

s2
contacting said fixed chromosomes under hybridizing conditions with said set
of clones or DNA fragments or oligo- or polynucleotides, permitting specific
hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to
said locus or loci in said chromosome of interest;

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detecting non-radioactively any of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1475. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein said clones or fragments or said oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprises one or more detectable non-radioactive modified or labeled nucleotides incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

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wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to BASE at a position other than the C5 position when
BASE is a pyrimidine or a pyrimidine analog, at a position other than the C8
position when BASE is a purine or a purine analog, and at a position other than the
C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM directly or through a linkage group; and
Sig is covalently attached to SM directly or through a linkage group;

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
wherein PM is covalently attached to SM directly or through a linkage group;
Sig is covalently attached to PM directly or through a linkage group;

K52
fixing the chromosomes from or in said cell;

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contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting non-radioactively any of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1476. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments or oligo- or polynucleotides derived from said clones, wherein said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest and each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM-SM-BASE-Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety.

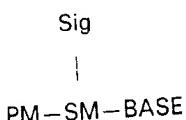
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wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached to BASE at a position other than the C5 position when
BASE is a pyrimidine moiety or a pyrimidine analog, at a position other than the C8
position when BASE is a purine or a purine analog, and at a position other than the
C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

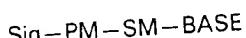
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and
Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM,
and Sig is covalently attached to PM directly or through a linkage group;

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contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

X⁵²
detecting non-radioactively any of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generated signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

X⁵³
1499. (Amended) The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X⁵⁴
1507. (Amended) The process according to claim 1504, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X⁵⁵
1565. (Amended) The process according to claim 1564, wherein said detecting step is carried out by means of a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a cherniluminescent compound and an electron dense compound.

1566. (Amended) The process according to claim 1564, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

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1570. (Twice Amended) The process according to any of claims 1473, 1474,
1475 or 1476, wherein said Sig detectable non-radioactive moiety is capable of
being detected by a member selected from the group consisting of an enzymatic
measurement, a fluorescent measurement, a chemiluminescent measurement, a
microscopic measurement and an electron density measurement.

1582. (Twice Amended) A process for preparing a detectable non-radioactively
labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable non-radioactive chemically modified or
labeled nucleotides or nucleotide analogs, which nucleotide analogs can be
attached to or coupled to or incorporated into DNA or RNA or an oligo- or
polynucleotide of interest, alone or in conjunction with one or more other
modified or unmodified nucleic acids selected from the group consisting of
nucleotides, oligonucleotides and polynucleotides, wherein said other
modified or unmodified nucleic acids are capable of incorporating into an
oligo- or polynucleotide of interest, and wherein said detectable non-
radioactive chemically modified or labeled nucleotides or nucleotide analogs
comprise one or more signaling moieties which are capable of providing
directly or indirectly a detectable non-radioactive signal; or

(2) an oligo- or polynucleotide of interest comprising one or more
said detectable non-radioactive chemically modified or labeled nucleotides or
nucleotide analogs, alone or in conjunction with one or more other modified
or unmodified nucleic acids selected from the group consisting of
nucleotides, oligonucleotides and polynucleotides;

wherein said detectable non-radioactive chemically modified or labeled nucleotides
or nucleotide analogs have been modified or labeled on at least one of the sugar
moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base
moiety or the base analog, and are selected from the group consisting of:

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(i)

PM-SM-BASE-Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of
any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to
SM, and Sig is covalently attached to BASE directly or through a linkage group at a
position other than the C5 position when BASE is a pyrimidine moiety or an analog
thereof, at a position other than the C8 position when BASE is a purine moiety or
an analog thereof, and at a position other than the C7 position when BASE is a 7-
deazapurine moiety or an analog thereof;

(ii)

Sig

|

PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of
any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently
attached to SM, and Sig is covalently attached to SM directly or through a linkage
group; and

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(iii)

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of
any of the foregoing, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM,
and Sig is covalently attached to PM directly or through a linkage group;
provided that when said nucleotide or nucleotide analog (iii) is attached to an
oligonucleotide or a polyribonucleotide, and provided that when Sig is attached
through a chemical linkage to a terminal PM at the 3' position of a terminal
ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal
oxidation of a 3' terminal ribonucleotide previously attached to said
oligonucleotide or polyribonucleotide; and

said oligo- or polynucleotide of interest; and

(B) either incorporating said one or more detectable non-radioactive chemically
modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or
polynucleotide, and preparing a non-radioactive labeled oligo- or polynucleotide of
interest, or preparing said oligo- or polynucleotide of interest from said oligo- or
polynucleotide recited in step (A)(2) above.

X52
X58
1608. (Amended) The process according to claim 1582, wherein said one or more
detectable non-radioactive chemically modified nucleotides or said other modified or
unmodified nucleic acids comprise a nucleoside di- or tri-phosphate.

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X59
1624. (Amended) The process according to claim 1623, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X60
1628. (Amended) The process according to claim 1627, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X61
1632. (Amended) The process according to claim 1631, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X62
1639. (Amended) The process according to claim 1582, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X63
1647. (Amended) The process according to claim 1645, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X64
1686. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

1687. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when it is attached to the nucleotide directly or through a linkage group.

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X64
1688. (Amended) The process according to claim 1687, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X65
1696. (Amended) The process according to claim 1695, wherein said directly detectable signal providing Sig detectable non-radioactive moiety is selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound, an electron dense compound and an enzyme.

X66
1699. (Twice Amended) The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

Sub 21
1700. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

X67
providing or generating non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;
subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

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x 67
~~detecting the presence of each of said separated or resolved fragments by
means of the detectable radioactive signal provided by a radioactive metal chelated
by said chelating compounds or chelating components in the detectable non-
radioactive modified or labeled nucleotides or nucleotide analogs, and determining
the sequence of said nucleic acid of interest.~~

x 68
1701. (Twice Amended) A process for determining the sequence of a nucleic acid
of interest, comprising the steps of:

Sub 2
~~providing or generating detectable non-radioactive labeled nucleic acid
fragments, each fragment comprising a sequence complementary to said nucleic
acid of interest or to a portion thereof, wherein each of said fragments comprises
one or more detectable non-radioactive modified or labeled nucleotides or
nucleotide analogs, which nucleotide analogs can be attached to or coupled to or
incorporated into DNA or RNA, wherein said detectable non-radioactive modified or
labeled nucleotides or nucleotide analogs comprise one or more chelating
compounds or chelating components capable of chelating a radioactive metal and
providing a detectable radioactive signal, and wherein said one or more detectable
non-radioactive modified or labeled nucleotides or nucleotide analogs have been
modified or labeled on at least one of the sugar moiety, the sugar analog, the
phosphate moiety, the phosphate analog, the base moiety, or the base analog
thereof;~~

~~introducing or subjecting said fragments to a sequencing gel;
separating or resolving said fragments in said sequencing gel; and
detecting each of the separated or resolved fragments by means of the
detectable radioactive signal provided by a radioactive metal chelated by said
chelating compounds or chelating components in the detectable non-radioactive
modified or labeled nucleotides or nucleotide analogs, and determining the
sequence of said nucleic acid of interest.~~

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1702. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

radioactively detecting with a sequencing gel the detectable non-radioactive labeled nucleic acid fragments by means of a radioactive metal chelated by said chelating compounds or chelating components; and

determining the sequence of said nucleic acid of interest.

X68
1703. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

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1704. (Twice Amended) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising the steps of:

(A) providing

- (i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or
- (ii) one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs; or
- (iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

- (B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides (ii), or both (i) and (ii), into said one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, said detectable non-radioactive labeled fragments further comprising one or more detectable non-radioactive

✓68

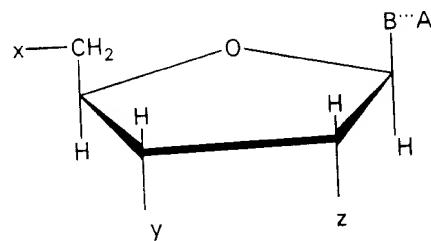
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chemically modified nucleotides or nucleotide analogs selected from the group
consisting of:



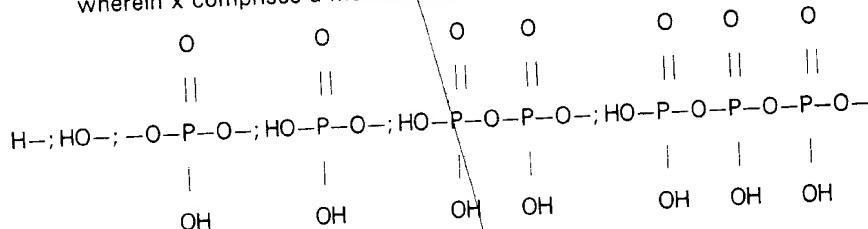
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine
moiety, or an analog of any of the foregoing, and B is covalently bonded to the
C1'-position of the sugar moiety or sugar analog, provided that whenever B is a
purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the
sugar moiety or sugar analog is attached at the N9 position of the purine moiety,
the purine analog, the 7-deazapurine moiety or the 7-analog thereof, and whenever
B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is
attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one
component of a signalling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing directly or
indirectly a detectable radioactive signal; and

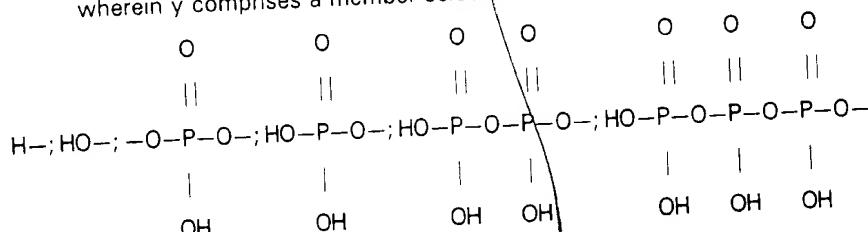
wherein B and A are covalently attached directly or through a linkage group,

and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



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wherein z comprises a member selected from the group consisting of

H- and HO-

(ii)

Sig

PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog.

SM is a sugar moiety or sugar analog.

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

{iii}

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog.

SM is a sugar moiety or sugar analog.

BASE is a base moiety or base analog.

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said labeled fragments to a sequencing gel;

(D) separating or resolving said labeled fragments; and

Fnz-5(D8)(C2)

X68

(E) detecting directly or indirectly the presence of said labeled
fragments by means of a radioactive metal chelated by said chelating compounds
or chelating components.

X69
1705. (Amended) A process for detecting a nucleic acid of interest in a sample,
which process comprises the steps of:

Sub 23
(a) specifically hybridizing said nucleic acid of interest in the sample with one or
more oligo- or polynucleotides, each such oligo- or polynucleotide being
complementary to or capable of hybridizing with said nucleic acid of interest or a
portion thereof, wherein said oligo- or polynucleotides comprise one or more
detectable non-radioactive modified or labeled nucleotides or nucleotide analogs,
which nucleotide analogs can be attached to or coupled to or incorporated into
DNA or RNA, and wherein said detectable non-radioactive modified or labeled
nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base
analog of any of the foregoing; and

Sig is a signaling moiety comprising a chelating compound or component
capable of chelating a radioactive metal and providing a detectable radioactive
signal, wherein PM is covalently attached to SM, BASE is covalently attached to
SM, and Sig is covalently attached to BASE directly or through a linkage group at a
position other than the C5 position when BASE is a pyrimidine moiety or an analog
thereof, at a position other than the C8 position when BASE is a purine moiety or
analog thereof and at a position other than the C7 position when BASE is a 7-

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deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

- (ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or component capable of providing chelating a radioactive metal and a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

- (iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or components capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

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provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting radioactively the presence of said signaling moieties Sig in any of the oligo- or polynucleotides which have hybridized to said nucleic acid of interest by means of a radioactive metal chelated by said chelating compounds or chelating components.

1706. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

- (i) an oligo- or polynucleotide having two segments:
 - (a) a first segment complementary to and capable of hybridizing to a portion of said nucleic acid of interest; and
 - (b) a second segment comprising at least one protein binding sequence; and
- (ii) a detectable protein capable of binding to said protein binding sequence and comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said detectable protein (ii) to form a complex;

(C) detecting radioactively the presence of said protein in said complex and said nucleic acid of interest by means of a radioactive metal chelated by said chelating compound or chelating component.

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X70
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1707. (Twice Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

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(ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

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detecting radioactively the signal generated by said specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides by means of a radioactive metal chelated by said chelating compound or chelating component, and determining the number of copies of said particular chromosome; and

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comparing said determined number of copies of said particular chromosome
with a number of copies of said particular chromosome determined for a normal cell
containing said particular chromosome, and determining whether the number of
copies of said particular chromosome in said cell is abnormal.

X71
1708. (Amended) A process for identifying a chromosome of interest in a cell
containing other chromosomes, the process comprising the steps of:

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providing a set of clones or DNA fragments, or oligo- or polynucleotides
derived from said clone or clones, wherein said clones or fragments or oligo- or
polynucleotides are specifically hybridizable to a locus or loci in said chromosome
of interest, wherein said clones or fragments or oligo- or polynucleotides comprise
one or more detectable modified or labeled nucleotides or nucleotide analogs, which
nucleotide analogs can be attached to or coupled to or incorporated into DNA or
RNA, and wherein said modified or labeled nucleotides or nucleotide analogs are
selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing a detectable
radioactive signal, wherein PM is covalently attached to SM, BASE is covalently
attached to SM, and Sig is covalently attached to BASE at a position other than the
C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position
other than the C8 position when BASE is a purine moiety or an analog thereof, and

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at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

- (ii) a nucleotide or nucleotide analog having the formula

Sig

|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

- (iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

X? wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1709. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs capable of detection, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analogs are selected from the group consisting of:

- (i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

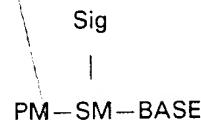
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing a detectable
radioactive signal, wherein PM is covalently attached to SM, BASE is covalently
attached to SM, and Sig is covalently attached to BASE at a position other than the
C5 position when BASE is a pyrimidine, or a pyrimidine analog, at a position other
than the C8 position when BASE is a purine or a purine analog, and at a position
other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog
thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

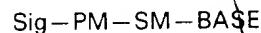
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

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Sig is a signaling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing a detectable
radioactive signal, wherein PM is covalently attached to SM, BASE is covalently
attached to SM, and Sig is covalently attached to SM directly or through a linkage
group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1710. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

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(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

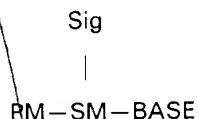
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing a detectable
radioactive signal, wherein PM is covalently attached to SM, BASE is covalently
attached to SM, and Sig is covalently attached to BASE at a position other than the
C5 position when BASE is a pyrimidine moiety or a pyrimidine analog, at a position
other than the C8 position when BASE is a purine or a purine analog, and at a
position other than the C7 position when BASE is a 7-deazapurine or a 7-
deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base
analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating
component capable of chelating a radioactive metal and providing a detectable
radioactive signal, wherein PM is covalently attached to SM, BASE is covalently
attached to SM, and Sig is covalently attached to SM directly or through a linkage
group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

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detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signals generated by each of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generate signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

1711. (Amended) A process for preparing a labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached

to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, or

(2) an oligo- or polynucleotide of interest comprising one or more of said detectable chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides,

wherein said chemically modified or labeled nucleotides or nucleotide analogs are modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—\$M—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

\$M is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein PM is covalently attached to \$M, BASE is covalently attached to \$M, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or

an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)

Sig

PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a radioactive signal, and wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

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Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group, provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and said oligo- or polynucleotide of interest;

and

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cut
(B) either incorporating said one or more modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

X 72
1712. (Amended) A process for detecting the presence of a nucleic acid of interest in a sample, comprising the steps of:

providing or generating (i) one or more detectable non-radioactively labeled oligonucleotides or polynucleotides, each of said detectable non-radioactively labeled oligonucleotides or polynucleotides comprising a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to specifically hybridize therewith, wherein said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides comprise one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogues, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof, and (ii) a sample that may contain said nucleic acid of interest;

forming in liquid phase hybrids comprising said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest;

separating or resolving in a gel said formed hybrids; and

detecting non-radioactively the separated or resolved hybrids to detect the presence of said nucleic acid of interest.

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1725 (Amended) The process according to claim 1400, wherein said direct detection is carried out with the same indicator molecules.

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1726. (Amended) The process according to claim 1400, wherein said direct detection is carried out with different indicator molecules.

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